REMARKS

I. Status of the Claims

Claims 3, 28 and 29 are as originally presented.

Claims 9, 47 and 48 are as previously presented.

Claims 1, 2, 8, 12, 15-17, 19, 25-27, 46, 51, 87, 88, and 90-96 are currently amended. Amendments to claims 1, 2, 15, 16, 25-27, 87, 88, 90, 91, and 94-96, more specifically, the expressions "ghrelin having one or more conservative amino acid substitutions" and "unacylated ghrelin having one or more conservative amino acid substitutions" find support notably at pages 12 to 20 of the specification as filed; amendments to claims 1 and 46, notably the expressions "treating insulin resistance" and "reducing insulin resistance" find support notably at page 11, lines 6 to 23, at page 42, lines 1 to 28, in Table 4, in Table 5, in Figure 5, in Figure 6, in Figure 8, in Figure 9, as well as in claims 62 and 64 as filed; and amendments to claims 17, 19, 51, 92 and 93 find support notably in claims 17, 19, 51, 92 and 93 as filed.

Claims 4-7, 10, 11, 13, 14, 18, 20-24, 30-45, 49, 50, 52-86, and 89 have been canceled without prejudice or disclaimer.

Claims 1-3, 8, 9, 12, 15-17, 19, 25-29, 46-48, 51, 87, 88, and 90-96 are currently pending.

By this Amendment, no new matter has been added to the application.

II. Specification

At page 3 of this Office Action, the Examiner indicates that the listing of references in the specification at pages 43 to 50 is not a proper information disclosure statement and further indicates that unless the references have been cited in an Information Disclosure Statement, they have not been considered by the Examiner.

Applicants wish to indicate that the references listed at pages 43 to 50 of the Office Action have been cited in the Information Disclosure Statement filed at the USPTO on December 1, 2009 and

that this Information Disclosure Statement has been marked has having been considered by the Examiner.

III. Brief Description of the Drawings

At page 3 of this Office Action, the Examiner objects to the Brief Description of the Drawings for Figures 2, 3, 5 and 7 because the Examiner is of the view that the Brief Description of the Drawings for Figures 2, 3, 5 or 7 does not match with the legend.

In response, paragraphs [0043], [0044], [0046] and [0048] of the published application have been amended as follows: paragraph [0043] has been amended to specify "FIG 2A-2E" and to add a period at the end of the paragraph; paragraph [0044] has been amended to specify "FIG 3A-3E", paragraph [0046] has been amended to specify "FIG 5A-5E" and paragraph [0048] has been amended to specify "FIG 7A-7E". It is believed that these amendments overcome the Examiner's objection.

IV. Response to Claim rejection – 35 USC § 112 Written description

In this Office Action, the Examiner rejects claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 as failing to comply with the written description requirement. More specifically, the Examiner is of the view that the written description is not commensurate in scope with any **analog** of ghrelin or any **analog** of unacylated ghrelin.

In response, the term "analog" has been deleted from claims 1, 2, 15, 16, 25, 26, 27, 87, 88, 90, 91, 94, 95 and 96. This term has been replaced with the expression "ghrelin having one or more conservative amino acid substitutions" or the expression "unacylated ghrelin having one or more conservative amino acid substitutions". These expressions are supported by the specification as originally filed and by the general knowledge in the art, at least in the following manner:

- Page 12 of the description defines **unacylated ghrelin** as follows:

  ""Unacylated ghrelin" comprises a peptide that lacks the octanoyl modification at Ser-3 noted above. In an embodiment, unacylated ghrelin comprises the peptide set forth in SEQ ID NO: 2 below…

...

Naturally-occuring variations of unacylated ghrelin include peptides that contain substitutions, additions or deletions of one or more amino acids, which in embodiments may result from changes in the nucleotide sequence of the encoding ghrelin gene or its alleles thereof or due to alternative splicing of the transcribed RNA. It is understood that such changes do not substantially affect the antagonistic properties, nor the pharmacological and biological characteristics of unacylated ghrelin variant. The peptides may be in the form of salts; in embodiments the acidic functions of the molecule may be replaced by a salt derivative thereof, such as a trifuoroacetate salt."

- Starting at page 14, the description provides a discussion of **conservative substitutions**:

"Conservative substitutions of one or more amino acids in the primary sequence of unacylated ghrelin may provide structural analogs of the peptide. In order to derive analogs of varied (e.g. greater) potency, various methods may be used such as alanine scans, selective substitutions with D- amino acid or synthetic amino acids, truncation of the peptide sequence in order to find a "functional core" of the peptide, covalent addition of molecules to improve the properties of the peptide such as its serum stability, in vivo half life, potency, hydrophilicity or hydrophobicity and immunogenicity."

The Examiner will appreciate that the passages of the description referred to above are applicable to both ghrelin having one or more conservative amino acid substitutions and unacylated ghrelin having one or more conservative amino acid substitutions.

Additionally, the Examiner's attention is brought to a publication by van der Lely *et al.* (June 2004 - enclosed herewith) wherein Table 1 at page 428 shows the primary structure of ghrelin from domesticated species aligned to the human ghrelin. Table 1 shows conservative amino acid substituted ghrelin, thereby indicating that ghrelin having one or more conservative amino acid substitutions was known in the art at the time of filing of the present application.

In view of this, it would therefore be clear to a person skilled in the art that the inventors at the time the application was filed, had possession of "ghrelin having one or more conservative amino acid substitutions" and "unacylated ghrelin having one or more conservative amino acid

substitutions" and thus had possession of the invention claimed in amended claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 and in the claims dependent thereon.

In light of this, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection.

IV. Response to Claim rejection – 35 USC § 112 Scope of Enablement

In this Office Action, the Examiner rejects claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 as the Examiner is of the view that the specification, while being enabling for **treating** an insulin-associated parameter by administering in a subject a composition comprising a ghrelin and unacylated ghrelin, it does not reasonably provide enablement for "*(i)* ***preventing*** *insulin* ***deficiency*** *or preventing insulin associated parameter in a subject by administering a composition comprising a ghrelin or analog thereof or a fragment of SEQ ID NO: 1, and unacylated ghrelin or analog thereof or a fragment of SEQ ID NO: 2; or (ii) altering an insulin-associated parameter in a subject by administering* ***any analog*** *of ghrelin and* ***any analog*** *of unacylated ghrelin.*" [Emphasis added]

More specifically and for the reasons outlined at pages 8 and 9 of this Office Action, the Examiner is of the view that "prevention" of an insulin-associated parameter is highly unpredictable.

In response, claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 have been amended to delete the term **preventing**, thereby overcoming the Examiner's rejection in this respect.

For the reasons outlined at pages 9, 10 and 11 of this Office Action, the Examiner is also of the view that a person skilled in the art would require undue experimentation to make and then use all possible **analogs** of ghrelin and **analogs** of unacylated ghrelin for preventing and/or treating any insulin-associated parameter in a subject.

As indicated above, claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 have been amended so that they no longer refer to **analogs** of ghrelin and **analogs** of unacylated ghrelin, thereby overcoming the Examiner's rejection in this respect.

The expression "analog thereof" has been deleted from claims 1, 2, 15, 16, 25, 26, 27, 87, 88, 90, 91, 94, 95 and 96 and replaced with the expression "ghrelin having one or more conservative amino acid substitutions" or the expression "unacylated ghrelin having one or more conservative amino acid substitutions". Applicants submit that the specification as filed fully enables the expressions "ghrelin having one or more conservative amino acid substitutions" and "unacylated ghrelin having one or more conservative amino acid substitutions". Particularly, the description at pages 14, line 16 to page 20, line 17 defines conservative amino acid substitutions and describes how to obtain such substitutions. In view of the information provided in the present specification, a person skilled in the art would not require undue experimentation to make and use ghrelin having one or more conservative amino acid substitutions and unacylated ghrelin having one or more conservative amino acid substitutions and would not require undue experimentation to use those ghrelin and unacylated ghrelin having one or more conservative amino acid substitutions.

The Examiner relies on the teachings of Marzullo *et al.*, Flanagan *et al.*, Enomoto *et al.*, Mickle *et al.* and Adelhorst *et al.* in raising this rejection. In view of the amendments to the claims, the teachings of these documents are believed to be irrelevant.

It is submitted that the subject matter of claims 1 to 9, 11, 12, 15 to 20, 25 to 29, 43 to 48 and 87 to 96 is fully enabled by the specification as filed and in compliance with the requirements of 35 USC § 112, first paragraph.

In light of this, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection.

IV. Response to Claim rejection – Double Patenting

In this Office Action, the Examiner rejects claims 1 to 8, 11, 12, 17 to 20, 25 to 29, 43 to 48 and 87 to 96 for non-statutory obviousness-type double patenting as being unpatentable over claims 1 to 21 of U.S. Patent 7,485,620 (herein after referred to as "the '620 Patent") in view of Enomoto *et al.* and Flanagan *et al.*

Applicants submit that claims 1, 2, 3, 7, 8, 9, 12, 15, 16, 17, 19, 25, 26, 27, 28, 29, 46, 47, 48, 51, 87, 88, 90, 91, 92, 93, 94, 95 and 96 as currently amended are patentably distinct over the claims of the '620 Patent, Enomoto *et al.* and Flanagan *et al.* for at least the following reasons.

The claims of the present application are directed to a combination of ghrelin or ghrelin having one or more conservative amino acid substitutions and unacylated ghrelin or unacylated ghrelin having one or more conservative amino acid substitutions for use in treating insulin resistance and lowering glucose level.

Particularly, the present application teaches that co-administration of ghrelin and unacylated ghrelin exerts a **synergistic** effect so as to markedly **improve the actions of unacylated ghrelin in counteracting the actions of ghrelin** on glucose levels and insulin resistance. This synergistic effect is demonstrated notably in Figures 3 and 4 of the specification as filed, which show that co-injection of ghrelin and unacylated ghrelin lowers serum glucose levels significantly when compared to changes in glucose levels as seen after injection of unacylated ghrelin alone. Similarly, Figures 8 and 9 of the application as filed show that co-injection of ghrelin and unacylated ghrelin impressively improves insulin sensitivity when compared to injection of unacylated ghrelin alone.

Therefore, unacylated ghrelin, which counteracts the action of ghrelin, and ghrelin cooperate in an **unexpected** manner to modulate insulin-associated parameters.

Such cooperation is not rendered obvious by the claims of the '620 Patent which relate to the effects of unacylated ghrelin on glucose and insulin metabolisms.

Starting from the '620 Patent, a person skilled in the art would not be motivated to combine ghrelin to unacylated ghrelin to decrease insulin resistance and lower glucose levels at least because: 1) the '620 Patent shows that ghrelin **induces** an insulin resistance state (see, for example, Figures 2A and 2B of the '620 Patent), and 2) the '620 Patent shows that unacylated ghrelin alone counteracts the actions of ghrelin. A person skilled in the art would typically find counter-intuitive to use **ghrelin** to counteract the actions of **ghrelin**.

Furthermore, a person skilled in the art would not expect ghrelin and unacylated ghrelin to work together to produce an effect greater (synergy) then when unacylated ghrelin is used alone.

Enomoto *et al.* and Flanagan *et al.* do not mention unacylated ghrelin and do not provide any indication of its biological activity. These two documents do not provide any suggestion or motivation for a person skilled in the art to use a combination of ghrelin and unacylated ghrelin to treat insulin resistance and to lower glucose levels such as specified in the claims submitted herewith.

In view of these comments, Applicants respectfully submit that the claims of the present application define an invention that is unobvious and patentably distinct in view of the claims of the '620 Patent and Enomoto *et al.* and Flanagan *et al.*

In light of this, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection.

V. CONCLUSION

This application is believed to be in condition for allowance. A prompt and favorable action on the merits of the application is earnestly solicited.

Applicants believe no additional fee is due with this response other than the extension of time fee and the supplemental information disclosure statement fee, which are being paid herewith via credit card. However, if an additional fee is due or to credit any overpayment, please charge or credit our Deposit Account No. 08-0219, under Order No. 0290494.00122US1 from which the undersigned is authorized to draw.

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Respectfully submitted,

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